FLUORINE[1]

ACUTE EXPOSURE GUIDELINE LEVELS

[1]This document was prepared by the AEGL Development Team comprised of Sylvia Talmage (Oak Ridge National Laboratory) and the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances member Ernest Falke (Chemical Manager). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Subcommittee on Acute Exposure Guideline Levels. The NRC subcommittee concludes that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guidelines reports (NRC 1993; NRC 2001).

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. Three levels - AEGL-1, AEGL-2 and AEGL-3 — are developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

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EXECUTIVE SUMMARY

Fluorine is a reactive, highly irritating and corrosive gas used in the nuclear energy industry, as an oxidizer of liquid rocket fuels, and in the manufacture of various fluorides and fluorocarbons. Fluorine is a severe irritant to the eyes, mucous membranes, lungs, and skin; the eyes and the respiratory tract are the target organ/tissues of an acute inhalation exposure. Death is due to pulmonary edema. Data on irritant effects in humans and lethal and sublethal effects in five species of mammals (dog, rat, mouse, guinea pig, and rabbit) were available for development of AEGL values.

Regression analyses of the concentration-exposure durations (for the fixed endpoint of mortality) for all of the animal species reported in the key study (Keplinger and Suissa 1968) determined that the relationship between concentration and time is $C^n \times t = k$, where n = approximately 2 (actual value of n for the most sensitive species in irritation and lethality studies, the mouse, is 1.77). This concentration exposure duration relationship was applied to both the AEGL-2 and AEGL-3 levels because the irritant and corrosive action of fluorine on the respiratory tissues differs by only a matter of degree for these AEGL levels: (1) respiratory irritation with edema resulting in mild, reversible lung congestion, and (2) severe respiratory irritation resulting in severe lung congestion. Death results from acute pulmonary edema and consequent respiratory failure. Although the data base for fluorine is small, the data from the key study, augmented with data from several other studies, were considered adequate for derivation of the three AEGL classifications for five time periods.

The AEGL-1 was based on the observation that adult volunteers could tolerate exposure to 10 ppm for 15 minutes without irritant effects (Keplinger and Suissa 1968). Although this value is below the definition of an AEGL-1 (slight irritation), it provides the longest controlled exposure duration for which no irritation in humans was reported. An intraspecies uncertainty factor of 3 was applied because fluorine is highly corrosive to the tissues of the respiratory tract and effects are not expected to vary greatly among individuals, including susceptible individuals (NRC 2001). Although no data on asthmatics were found, the uncertainty factor of 3 was considered adequate to protect this sensitive subpopulation because the value was a NOAEL and because shorter-term, repeated exposures produced no substantially greater effects in healthy individuals. The value is supported by a second study in which volunteers “tolerated” exposure to 10 ppm for an undefined period of time (Belles 1965). A modifying factor of 2 was applied based on a limited data base and short exposure durations. The resulting value of 1.7 ppm was used across all AEGL-1 exposure durations because, at mildly irritating concentrations, adaptation to slight sensory irritation occurs. As noted, this value is supported by limited workplace monitoring data: workers exposed to fluorine at average yearly concentrations up to 1.2 ppm (range, 0.0-17 ppm) over a four-year period reported fewer incidences of respiratory complaints or diseases than a similar group of nonexposed workers (Lyon 1962). The workers are assumed to encompass a small range of sensitivity; the additional intraspecies uncertainty factor of 3 was considered sufficient to protect sensitive individuals.

Mild lung congestion was selected as the threshold for irreversible, long-lasting effects as defined by the AEGL-2. The AEGL-2 was based on an animal study in which mild lung congestion was observed in mice at 67 ppm for 30 minutes and 30 ppm for 60 minutes (Keplinger and Suissa 1968). Effects were slightly less serious in three other species. Although

concentrations causing irritant effects or lethality in three other species for the same time periods suggested similar species sensitivity, the mouse data, because of slightly lower values, were chosen as the basis for developing the AEGL-2 and AEGL-3. Similar sensitivity was observed among all species in the key study; therefore, an interspecies uncertainty factor of 1 was applied to address interspecies variability. Fluorine is a highly corrosive gas that reacts directly with the tissues of the respiratory tract, with no pharmacokinetic component involved in the toxicity; therefore, there is likely to be little difference among individuals in response to fluorine at concentrations that define the AEGL-2. The 30- and 60-minute values for the mouse were divided by an intraspecies uncertainty factor of 3 to protect sensitive individuals, since effects are not likely to differ greatly among individuals, and by a modifying factor of 2, based on a limited data base. The 30-minute value was time scaled to the 10-minute AEGL-2, and the 60-minute value was time scaled to the 4-hour AEGL-2 value. Time scaling was based on the $C^{1.77} \times t = k$ relationship. The value of n was derived from regression analysis of the mouse lethality data in the key study. The 8-hour-AEGL-2 value was set equal to the 4-hour value because at low concentrations the hygroscopic fluorine would react with and/or be scrubbed by the nasal passages, and because at mildly irritating concentrations, adaptation to sensory irritation occurs. The 10- and 30-minute AEGL-2 values are supported by studies in which human volunteers found short-term exposures to 15-25 ppm irritating to the eyes, nose, and throat (Rickey 1959; Keplinger and Suissa 1968).

The AEGL-3 values were derived from the highest exposures that resulted in no deaths in five species over 4 exposure durations (13 tests) for up to 45 days post exposure, but did produce severe lung congestion in the mouse (Keplinger and Suissa 1968). Severe lung congestion in the sensitive mouse was considered the threshold for lethality as defined by the AEGL-3. For the mouse, the 60-minute highest non-lethal value was 75 ppm. This value is one-half of the 60-minute LC_{50} value for the mouse. Because of the similar species sensitivity in the key study, based on both irritant effects and lethality, an interspecies uncertainty factor of 1 was considered sufficient to account for interspecies variability. The values were divided by an uncertainty factor of 3 to protect sensitive individuals (fluorine is a highly reactive, corrosive gas whose effect on respiratory tract tissues is not expected to differ greatly among individuals) and by a modifying factor of 2, based on a limited data base. Using the 60-minute value of 75 ppm, AEGL-3 values for the other exposure times were calculated based on the $C^{1.77} \times t = k$ relationship. The value of n was derived from regression analysis of the mouse lethality data in the key study. The 8-hour value was set equal to the 4-hour value because fluorine would react with or be scrubbed by the nasal passages at these fairly low time-scaled concentrations. The safety of setting the 8-hour value equal to the 4-hour value is supported by another study in which a 7-hour experimental exposure concentration of 100 ppm that resulted in an overall 60% mortality for four species (Eriksen 1945; Stokinger 1949) is higher than the extrapolated 7-hour LC_{50} values for the mouse (50 ppm) and rat (65 ppm) based on the Keplinger and Suissa (1968) study.

The calculated values are listed in the table below.

S 1. Summary of Proposed AEGL Values for Fluorine						
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**
AEGL–1[a,b] (Nondisabling)	1.7 ppm (2.6 mg/m^3)	1.7 ppm (2.6 mg/m^3)	1.7 ppm (2.6 mg/m^3)	1.7 ppm (2.6 mg/m^3)	1.7 ppm (2.6 mg/m^3)	No irritant effects - humans (Keplinger and Suissa 1968)
AEGL–2[c] (Disabling)	20 ppm (31 mg/m^3)	11 ppm (17 mg/m^3)	5.0 ppm (7.8 mg/m^3)	2.3 ppm (3.6 mg/m^3)	2.3 ppm (3.6 mg/m^3)	Mild lung congestion - mice (Keplinger and Suissa 1968)
AEGL–3 (Lethal)	36 ppm (56 mg/m^3)	19 ppm (29 mg/m^3)	13 ppm (20 mg/m^3)	5.7 ppm (8.8 mg/m^3)	5.7 ppm (8.8 mg/m^3)	Severe lung congestion - mice (Keplinger and Suissa 1968)

[a]The characteristic, pungent odor of fluorine will be noticeable at this concentration.
[b]The same value was used across all time periods because, at mildly irritating concentrations, adaptation to sensory irritation occurs.
[c]30-Minute and 1-hour values are based on separate data points.

1. INTRODUCTION

Fluorine belongs to the halogen group of elements; these elements do not occur in the elemental state in nature. When formed experimentally, fluorine is a pale yellow, diatomic gas (F_2) with a choking, irritating odor. Fluorine is used in the nuclear energy industry to produce gaseous uranium hexafluoride, as an oxidizer of liquid rocket fuels, and in the manufacture of various fluorides and fluorocarbons (Teitelbaum 2001).

Chemically, fluorine is the most electronegative of the halogens and is the most powerful oxidizing agent known (Teitelbaum 2001). It reacts vigorously with most oxidizable substances at room temperature, frequently with ignition. It also combines with most other elements to form fluorides. Reaction with water results in decomposition of the water and formation of hydrofluoric acid, oxygen (di)fluoride, hydrogen peroxide, oxygen, and ozone (O'Neil et al. 2001). Other relevant chemical and physical properties are listed in Table 1.

Fluorine is produced in an enclosed system of fluorine-generating cells. Anhydrous hydrogen fluoride, the basic starting material is mixed with potassium fluoride-hydrogen fluoride to form potassium bifluoride (KHF_2) which contains various concentrations of free hydrogen fluoride. Fluorine is produced by the electrolysis of anhydrous potassium bifluoride. Commercial fluorine plants operate in the United States, Canada, France, Germany, Italy, Japan, the United Kingdom, and South Africa. In 2003, the total commercial production capacity of fluorine in these countries was estimated at approximately 20,000 tons/year. Production data were unavailable for Russia and China. At most sites, elemental fluorine is used captively for the production of inorganic fluorides. The primary use of elemental fluorine is in the manufacture of uranium hexafluoride (Shia 2003).

TABLE 1. Chemical and Physical Data

Parameter	Value	Reference
Synonyms	Bifluoriden, fluor, fluorine-19, fluoro	HSDB 2003
Molecular formula	F_2	O'Neil et al. 2001
Molecular weight	37.99	O'Neil et al. 2001
CAS Registry Number	7782-41-4	HSDB 2003
Physical state	Pale, yellowish green gas	O'Neil et al. 2001
Vapor pressure	1 mm Hg @ -223EC >10 atm @ 20EC	HSDB 2003 Teitelbaum 2001
Flammability	Nonflammable; powerful oxidizing agent	AAR 1987
Density	1.695 (air = 1.29)	Lewis 1993
Melting point	-219.61EC	O'Neil et al. 2001
Boiling point	-188.13EC	O'Neil et al. 2001
Solubility	No data; reacts with water	O'Neil et al. 2001
Conversion factors	1 ppm = 1.55 mg/m^3 1 mg/m^3 = 0.64 ppm	ATSDR 2003

In the U.S., fluorine is packaged and shipped under pressure (415 psi) in steel cylinders conforming to Department of Transportation specifications. The size of cylinders containing pure fluorine is limited to 2.7 kg; cylinders containing mixtures of 10-20% fluorine in nitrogen can contain up to 500 kg fluorine (Shia 2003).

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No reports of lethal effects from acute inhalation exposure to fluorine were identified. At low concentrations, fluorine is extremely irritating to the nose and eyes.

2.2. Nonlethal Toxicity

No human studies documenting specific fluorine exposure levels and time of exposure were found for acute, irreversible effects. Limited data are available on reversible, non-disabling effects of fluorine gas to humans. In many of the studies, details of the exposures, particularly the exposure times, were not given. Fluorine has a characteristic, pungent odor (O'Neil et al. 2001). The odor threshold for fluorine is 0.10-0.20 ppm (Rickey 1959; Amoore and Hautala 1983). Available human data are summarized in Table 2 and discussed below.

Rickey (1959) reported on an outdoor spill test conducted by the U.S. Air Force. Two volunteers walked into the dispersed cloud downwind of a test spill. The measured concentration was 25 ppm which the men were able to tolerate; a specific exposure time was not stated. Following the exposure, both men developed sore throats and chest pains that lasted 6 hours. The author stated that 20-50 ppm cannot be tolerated by humans but did not give additional data to support the statement.

Belles (1965) reported a series of tests involving nine male volunteers. All tolerated repeated short-term exposure to 10 ppm without "intolerable" discomfort. Concentrations of 15 to 25 ppm caused some eye and nasal irritation to the majority of subjects after just three breaths. Skin exposure tests indicated that reaction with body hair and dermal irritation may be expected between 100 and 200 ppm.

Keplinger and Suissa (1968) exposed five adult volunteers (19-50 years of age) to concentrations up to 100 ppm via a face mask. These tests were designed to test for irritation only. A concentration of 10 ppm for up to 15 minutes was reported to be nonirritating to the eyes and nose. A concentration of 25 ppm for 5 minutes caused slight irritation to the eyes but could be inhaled without respiratory difficulty. A concentration of 50 ppm for 3 minutes was irritating to the eyes and slightly irritating to the nose. Concentrations of 67 to 100 ppm for one minute were irritating to the eyes and nose and became uncomfortable after a few seconds. The subjects reported the 67 ppm concentration as being less irritating than cigarette smoke in the eye. The subjects did not inhale at the 100 ppm concentration; inhalation exposure to 78 ppm caused coughing. The 100 ppm concentration caused slight irritation of the skin and a "sticky" feeling. According to the authors, the eyes were the most sensitive indicator of irritation in humans. Keplinger and Suissa (1968) also reported that a few repeated exposures at a concentration of 10 ppm for 3 to 5 minutes every 15 minutes over a two- to three-hour time period caused only slight irritation to the eyes and skin. No respiratory difficulty was reported.

TABLE 2. Summary of Irritant Effects in Humans			
Concentration (ppm)	**Exposure Time**	**Effects**	**Reference**
10	Not stated	"Tolerated"	Belles 1965
10	15 min	No irritation of eyes, nose, or respiratory tract	Keplinger and Suissa 1968
10	3-5 min every 15 min for 2-3 hours	slight irritation to the eyes and skin; no respiratory difficulty	Keplinger and Suissa 1968
15-25	Three breaths	Eye and nasal irritation	Belles 1965
25	not stated	Tolerated; sore throats and chest pains of 6 hours duration	Rickey 1959
25	5 min	Slight irritation to eyes, inhaled intermittently without difficulty	Keplinger and Suissa 1968
50	3 min	Irritating to eyes and slightly irritating to nose	Keplinger and Suissa 1968
67	1 min	Irritating to eyes and nose but not unbearable	Keplinger and Suissa 1968
78	1 min	Irritating to eyes and nose; caused coughing when inhaled	Keplinger and Suissa 1968
100	0.5 min	Very irritating to eyes and nose; no "after effects"	Keplinger and Suissa 1968
100	1 min	Very irritating to eyes and nose (subjects did not inhale); slightly irritating to the skin	Keplinger and Suissa 1968
100-200	not stated	Reaction with skin and body hair	Belles 1965

Lyon (1962) reported a lack of significant medical findings in 61 workers exposed to fluorine concentrations in excess of 0.1 ppm. Over a nine-year period, yearly average air concentrations ranged from 0.3 to 1.4 ppm (range <0.1 to 24.7 ppm). Workers were exposed either for 50-60% of their work time for periods of 7-9 months or 10% of their work time at the highest concentrations. Average daily urine fluorine excretion was 1.1 mg/L. Medical records of workers exposed to average yearly concentrations up to 1.2 ppm (range, 0.0-17 ppm) were evaluated for the last four years of exposure. These workers reported fewer incidences of respiratory complaints or diseases than a similar group of 2000-3000 nonexposed workers. Usefulness of the study is limited by the lack of fluorine determination in urine of unexposed workers and the inability of the measurement technique to differentiate between fluorine and hydrogen fluoride. However, the author noted that samples were taken only when the characteristic odor of fluorine was present and the characteristic odor of hydrogen fluoride was absent. In contrast, Machle and Evans (1940) reviewed several monitoring studies in which undefined exposures to fluorine in industry resulted in increased asthmatic attack frequency over that in the non-exposed population.

There is potential for individuals to become sensitized to halogens following acute exposure. A review of studies on drinking water fluoridation and a study with rabbits treated with sodium fluoride did not indicate that immune reactions occurred (ATSDR 2003).

2.3. Developmental/Reproductive Toxicity

No studies were located regarding reproductive or developmental effects in humans after inhalation exposure to fluorine. Fluoride is rapidly absorbed following oral ingestion, crosses

the placenta in limited amounts, and is found in placental and fetal tissue (ATSDR 2003). Studies on the incidence of reproductive or developmental effects in areas using fluoridated water have found no correlation between fluoridation levels and birth defects (ATSDR 2003).

2.4. Genotoxicity

No data concerning the genotoxicity of fluorine in humans were identified in the available literature.

2.5. Carcinogenicity

Although several studies indicated an increase in respiratory cancers among workers engaged in several industries where they could be exposed to hydrogen fluoride or fluoride dusts, the concomitant exposure to other chemicals and smoking status of the workers, along with the lack of clear exposure concentration make the studies of questionable relevance (ATSDR 2003). There is no carcinogenicity data for fluoride gas.

2.6. Summary

No human data involving acute lethal exposures were located. Limited data are available on reversible, non-disabling effects of fluorine gas to humans. In many of the studies, details of the exposures, particularly the duration of exposure, were not given. In a fairly well reported study with human volunteers, 10 ppm for 15 minutes caused no irritation of the eyes, nose, or respiratory tract and 10 ppm for 3 to 5 minutes every 15 minutes for 2 to 3 hours caused slight irritation to the eyes and skin but no respiratory difficulty.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Data on acute lethal concentrations of fluorine for exposure durations of 5 minutes to 7 hours are available for the rat, mouse, guinea pig, and rabbit. A study with the dog involved repeated exposure. Data on single acute exposures are summarized in Table 3.

3.1.1. Dogs

No studies on single exposures were located. In short-term, repeated exposures, groups of five dogs (sex and strain unspecified) were administered fluorine at concentrations of 0.5, 2, 5, and 16 ppm for up to 35 days (Stokinger 1949). The exposure regime (not stated) was apparently 5-6 hours/day, 5 days/week for a total exposure of 170 hours. Concentrations were estimated by metering; no analyses were made. At the two higher concentrations, dogs exhibited seizures followed by death. At the 16 ppm exposure, mortality was 100% by the 60^{th} hour of exposure. No toxic symptoms and no deaths were observed at the two lower concentrations. Histological changes included moderate to moderately severe hemorrhage and liver congestion in 4 of 4 animals at 16 ppm, red discoloration of the lungs, mild bronchitis, and bronchiectasis in 4 of 5 dogs at 5 ppm, pulmonary hemorrhage and edema in 2 of 5 dogs at 2 ppm, and no consistent significant damage at 0.5 ppm.

3.1.2. Rats

Eriksen (1945) and Stokinger (1949) reported the same study in which a fluorine concentration of 10,000 ppm for an exposure time of 5 minutes was fatal to rats (sex and strain unspecified) within 24 hours, with the majority of deaths occurring by the end of the exposure period. Thirty minutes of exposure to 1000 ppm caused 87% mortality and mortality reached 100% by 14 days post exposure. A concentration of 500 ppm for one hour caused 90% mortality by the end of the exposure period. Percent mortality increased at 24 hours post exposure, and at 14 days, all animals were dead. By 4 days post exposure, mortality was 100% for rats exposed to 200 ppm for 3 hours. At 14 days after exposure to 100 ppm for 7 hours, 54% of the animals were dead.

TABLE 3. Summary of Acute Lethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect[a]	Reference
Rat	10,000	5 min	100% mortality	Eriksen 1945; Stokinger 1949
	1000	30 min	100% mortality	
	500	1 h	100% mortality	
	200	3 h	100% mortality	
	100	7 h	54% mortality	
Rat	700	5 min	LC_{50}	Keplinger and Suissa 1968
	390	15 min	LC_{50}	
	270	30 min	LC_{50}	
	185	1 h	LC_{50}	
Mouse	10,000	5 min	100% mortality	Eriksen 1945; Stokinger 1949
	1000	30 min	100% mortality	
	500	1 h	100% mortality	
	200	3 h	100% mortality	
	100	7 h	96% mortality	
Mouse	600	5 min	LC_{50}	Keplinger and Suissa 1968
	375	15 min	LC_{50}	
	225	30 min	LC_{50}	
	150	1 h	LC_{50}	
Guinea pig	10,000	5 min	100% mortality	Eriksen 1945; Stokinger 1949
	1000	30 min	100% mortality	
	500	1 h	100% mortality	
	200	3 h	90% mortality	
	100	7 h	no mortality	
Guinea pig	395	15 min	LC_{50}	Keplinger and Suissa 1968
	170	1 h	LC_{50}	
Rabbit	10,000	5 min	100% mortality	Eriksen 1945; Stokinger 1949
	1000	30 min	100% mortality	
	500	1 h	100% mortality	
	200	3 h	100% mortality	
	100	7 h	88% mortality	
Rabbit	820	5 min	LC_{50}	Keplinger and Suissa 1968
	270	30 min	LC_{50}	

[a] LC_{50} and 100% mortality values were obtained at 14 days post exposure.

Autopsy results indicated that fluorine gas was severely corrosive to the respiratory tract as shown by bronchial and alveolar necrosis. Death was attributed to respiratory failure resulting from acute pulmonary damage involving edema, emphysema, and hemorrhage. Gross

observations of animals surviving the 100 and 200 ppm concentrations and sacrificed 14 days post exposure revealed that lung damage was either slight or had undergone substantial repair. Kidney abnormalities including general engorgement, slight edema, slight swelling of the cortex and inflammation of the medulla were observed (frequency not stated) at 14 days post exposure but not at the end of the exposure period. Technical problems in monitoring fluorine gas levels make the quantitative exposure level data unreliable in this study; however, qualitative results from these experiments are useful.

Keplinger and Suissa (1968) exposed groups of 10 Osborne-Mendel rats (sex unspecified) to measured concentrations of fluorine for periods of 5, 15, 30, or 60 minutes. The LC_{50} values were 700, 390, 270, and 185 ppm, respectively. Few signs of intoxication were observed immediately after exposure except for irritation of the eyes and nose. Death occurred approximately 12 to 18 hours after exposure. A few deaths were recorded after 24 hours. Animals that lived for 48 hours post exposure generally survived the 14-day observation period. Animals exposed to high concentrations died of respiratory failure with the lungs showing diffuse congestion and hemorrhage; no damage occurred in other organs. No deaths were reported in rats tested at 50% of the LC_{50} for each of the time periods.

Repeated daily exposures of rats (sex and strain unspecified) to concentrations of 0.5, 2, 5, and 16 ppm were conducted over a period of 21-35 days (Stokinger 1949). The exposure regime (not stated) was apparently 5-6 hours/day, 5 days/week. Rats exposed at the two highest concentrations had symptoms of coarsening and stiffening of the fur and irritation of the eyes and nose; these symptoms were mild at the two lower concentrations. Mortalities at the end of the exposure period were 0, 8, 27, and 50% at 0.5, 2, 5, and 16 ppm, respectively. A 10% weight loss occurred at the 16 ppm exposure concentration, but weight gains occurred at the lower exposure concentrations. Blood and hematology parameters were unchanged at all concentrations. Severe pulmonary irritation, oral lesions, and testicular degeneration occurred at 16 ppm; no grossly observable lung changes occurred at the two lower concentrations.

3.1.3. Mice

Eriksen (1945) and Stokinger (1949) exposed mice (sex and strain unspecified) to fluorine concentrations ranging from 100 to 10,000 ppm for 7 hours to 5 minutes, respectively. Concentrations of 10,000 ppm for 5 minutes, 1000 ppm for 30 minutes, 500 ppm for 1 hour, and 200 ppm for 3 hours were 100% fatal by the end of a 14-day post-exposure period. A concentration of 100 ppm for 7 hours resulted in 96% mortality. The majority of animals that died did so by the end of the exposure period. Autopsies indicated that fluorine gas was severely corrosive to the respiratory tract as shown by edema, emphysema, and hemorrhage. Death was attributed to respiratory failure resulting from acute pulmonary damage. As noted in Section 3.1.2., technical problems in monitoring fluorine gas levels make the quantitative exposure level data unreliable; however, qualitative results from these experiments are useful.

Keplinger and Suissa (1968) exposed groups of 10 Swiss-Webster mice (sex unspecified) to measured concentrations of fluorine for periods of 5, 15, 30, or 60 minutes. The LC_{50} values for the mice for the four respective time intervals were 600, 375, 225, and 150 ppm. Few signs of intoxication were observed immediately after exposure except for irritation of the eyes and nose. Death occurred approximately 12 to 18 hours after exposure. A few deaths were recorded after 24 hours. Animals that lived for 48 hours post exposure generally survived the 14-day

observation period. No deaths were reported in mice tested at 50% of the LC_{50} for each of the time periods. Animals exposed to high concentrations died of respiratory failure with the lungs showing diffuse congestion and hemorrhage; no damage occurred in other organs.

3.1.4. Guinea pigs

Eriksen (1945) and Stokinger (1949) exposed guinea pigs (sex and strain unspecified) to fluorine concentrations ranging from 100 to 10,000 ppm for exposure times of 7 hours to 5 minutes, respectively. Concentrations of 10,000 ppm for 5 minutes, 1000 ppm for 30 minutes, and 500 ppm for 1 hour were 100% fatal by the end of a 14-day post exposure period. A concentration of 200 ppm for 3 hours resulted in 90% mortality, and a concentration of 100 ppm for 7 hours resulted in no mortality. The majority of animals that died did so by the end of the exposure period. Autopsies indicated that fluorine gas was severely corrosive to the respiratory tract as shown by edema, emphysema, and hemorrhage. Death was attributed to respiratory failure resulting from acute pulmonary damage. Sublethal concentrations produced gross changes in the liver and kidneys (not further described). As noted in Section 3.1.2., technical problems in monitoring fluorine gas levels make the quantitative exposure level data unreliable; however, qualitative results from these experiments are useful.

Keplinger and Suissa (1968) exposed groups of five New England guinea pigs (sex unspecified) to measured concentrations of fluorine for periods of 15 or 60 minutes. LC_{50} values were 395 ppm at 15 minutes and 170 ppm at 60 minutes. Few signs of intoxication were observed immediately after exposure except for irritation of the eyes and nose. Cause of death and organ pathology were the same as discussed for the rat and mouse above.

3.1.5. Rabbits

Eriksen (1945) and Stokinger (1949) exposed rabbits (sex and strain unspecified) to fluorine concentrations ranging from 100 to 10,000 ppm for 7 hours to 5 minutes, respectively. Concentrations of 10,000 ppm for 5 minutes, 1000 ppm for 30 minutes, 500 ppm for 1 hour, and 200 ppm for 3 hours were 100% fatal by the end of a 14-day post exposure period. A concentration of 100 ppm for 7 hours resulted in 88% mortality. The majority of animals that died did so by the end of the exposure period. Autopsies indicated that fluorine gas was severely corrosive to the respiratory tract as shown by edema, emphysema, and hemorrhage. In rabbits, pulmonary hemorrhage was a more important component of lung damage than in other species. Death was attributed to respiratory failure resulting from acute pulmonary damage. "Infectious processes" were present in the lungs of some survivors. As noted in Section 3.1.2., technical problems in monitoring fluorine gas levels make the quantitative exposure level data unreliable; however, qualitative results from these experiments are useful.

Keplinger and Suissa (1968) exposed groups of 5 New England rabbits (sex unspecified) to measured concentrations of fluorine for two time periods. LC_{50} values for exposures of 5 and 30 minutes were 820 and 270 ppm, respectively. Clinical signs and organ pathology were the same as for the rat and mouse discussed above.

In short-term, repeated exposures, rabbits (sex and strain unspecified) were administered fluorine at concentrations of 0.5, 2, 5, and 16 ppm for up to 35 days (Stokinger 1949). The exposure regime was not stated, but was presumably 5 hours/day for a total exposure of 170

hours. At the two higher concentrations, mortality was 100%; at 2 ppm, 2 of 10 rabbits died; and at 0.5 ppm, 1 of 18 rabbits died. Histological changes included liver congestion and moderate to moderately severe lung hemorrhage in 4 of 4 animals at 16 ppm and moderate pulmonary irritation and slight liver damage in 4 of 5 animals at 5 ppm. At 2 ppm there was mild bronchial inflammation in 3 of 4 animals, and at 0.5 ppm there was little or no pulmonary damage.

3.2. Nonlethal Toxicity

Studies conducted at concentrations that were less than lethal are summarized in Table 4. Data are presented for the dog, rat, mouse, guinea pig, and rabbit. The latter four species were exposed to concentrations approximating 50, 25, and 12.5% of their respective LC_{50} values for exposure durations of 5, 15, 30, and 60 minutes.

3.2.1. Dogs

Dogs (sex and strain unspecified) exposed to 93 ppm for 60 minutes had symptoms of irritation, cough, slight labored breathing, and vomiting (Keplinger and Suissa 1968). Examinations at 7 to 14 days post exposure revealed small areas of hemorrhage in the lungs. Dogs exhibited only eye irritation at an exposure of 68 ppm for 1 hour. No irritation or gross pathologic changes in the lung were evident following exposure to 38 ppm for 1 hour. In short-term, repeated exposures, dogs treated with fluorine at a concentration of 0.5 ppm for up to 35 days (presumably 5 hours/day) showed no significant lung damage (Stokinger 1949).

TABLE 4. Summary of Sublethal Effects in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect[a]	Reference
Dog	93	1 h	irritation, cough, slight labored breathing, vomiting, small areas of hemorrhage in lungs	Keplinger and Suissa 1968
	93	15 min	slight lung congestion	
	68	1 h	eye irritation	
	38	1 h	no effect	
Rat	500	5 min	marked signs of intoxication, severe changes in lungs	Keplinger and Suissa 1968; Keplinger 1969
	350	5 min	moderate lung congestion	
	325	5 min	moderate lung congestion	
	175	5 min	labored breathing; mild lung congestion	
	150	5 min	very mild lung congestion	
	88	5 min	no effect	
Rat	195	15 min	irritation, labored breathing, moderate diffuse congestion	Keplinger and Suissa 1968
	98	15 min	very mild lung congestion	
	49	15 min	no effect	
Rat	140	30 min	irritation of eyes and nose, slight labored breathing, moderate diffuse lung congestion	Keplinger and Suissa 1968; Keplinger 1969
	68, 70	30 min	very mild lung congestion	
	35	30 min	no effect	

TABLE 4. Summary of Sublethal Effects in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect[a]	Reference
Rat	140	1 h	severe diffuse lung congestion, kidney and liver changes	Keplinger and Suissa 1968; Keplinger 1969
	93	1 h	eye irritation and labored breathing; mild diffuse lung congestion	
	75	1 h	mild diffuse lung congestion	
	47	1 h	very mild diffuse lung congestion	
	28	1 h	no effect	
Mouse	467	5 min	marked irritation of eyes and respiratory tract, labored breathing, severe diffuse lung congestion	Keplinger and Suissa 1968; Keplinger 1969
	321	5 min	moderate diffuse lung congestion	
	300	5 min	eye irritation and labored breathing; moderate diffuse lung congestion	
	174	5 min	slightly labored breathing; very mild diffuse lung congestion	
	130	5 min	very mild lung congestion	
	79	5 min	no effect	
Mouse	350, 359	15 min	severe diffuse lung congestion to congestion with hemorrhages	Keplinger and Suissa 1968; Keplinger 1969
	265, 285	15 min	moderate diffuse lung congestion	
	188	15 min	eye irritation and labored breathing moderate diffuse lung congestion	
	87	15 min	very mild diffuse lung congestion	
	65	15 min	no effect	
Mouse	113	30 min	eye irritation and labored breathing; mild diffuse lung congestion	Keplinger and Suissa 1968; Keplinger 1969
	64, 67	30 min	very mild lung congestion	
	32	30 min	no effect	
Mouse	75	1 h	eye irritation and labored breathing, severe diffuse lung congestion	Keplinger and Suissa 1968; Keplinger 1969
	55	1 h	very mild lung congestion	
	50	1 h	labored breathing; mild diffuse lung congestion	
	30	1 h	very mild diffuse lung congestion	
	15	1 h	no effect	
Guinea pig	198	15 min	eye irritation and labored breathing; mild diffuse lung congestion	Keplinger and Suissa 1968
	70	15 min	no effect	
Guinea pig	135	1 h	eye irritation and labored breathing; mild diffuse lung congestion	Keplinger and Suissa 1968
	73	1 h	no effect	
Guinea pig	100	7 h	severe damage to the respiratory system	Eriksen 1945; Stokinger 1949
Rabbit	410	5 min	eye irritation and labored breathing; moderate diffuse lung congestion	Keplinger and Suissa 1968
	134	5 min	slightly labored breathing	
	51	5 min	no effect	
Rabbit	135	30 min	eye irritation, very mild diffuse congestion	Keplinger and Suissa 1968
	71	30 min	no irritation, very mild diffuse congestion	
	32	30 min	no effect	

[a] Measured up to 45 days post exposure; serial sacrifice revealed that effects did not become worse with time and, in some cases, lung changes showed some regression starting 7 days post exposure.

3.2.2. Rats

Sublethal effects of inhalation exposure to fluorine were assessed in Osborne-Mendel rats (sex unspecified) exposed to concentrations of 500 ppm and 350 ppm (71% and 50% of the 5-minute LC_{50} values) for 5 minutes, 195 ppm (50% of the 15-minute LC_{50}) for 15 minutes, and 140 ppm (50% of the 30-minute LC_{50}) for 30 minutes (Keplinger and Suissa 1968). Very few signs of intoxication were observed immediately after exposure. Rats exposed to these concentrations experienced marked irritation of the eyes and respiratory tract immediately after exposure, and labored breathing and lethargy were observed several hours later. At sacrifice (up to 45 days post exposure), there was moderate to severe diffuse congestion of the lungs.

Sublethal exposures produced kidney and liver damage (Keplinger and Suissa 1968). Kidney damage was characterized by focal areas of coagulation necrosis in the cortex and focal areas of lymphocytic infiltration throughout the cortex and medulla. Liver damage included coagulation necrosis, periportal hemorrhages, and diffuse cloudy swelling. Kidney damage occurred at the same concentrations as lung involvement. Liver involvement occurred only at the highest sublethal concentrations. No-effect concentrations for organ pathology were 79 ppm for 5 minutes, 65 ppm for 15 minutes, 51 ppm for 30 minutes, and 30 ppm for 60 minutes.

Mild effects of inhalation exposure to fluorine were assessed in rats exposed to concentrations equal to 25% of the LC_{50} values for exposure times of 5, 15, 30, and 60 minutes (175, 98, 70, and 47 ppm, respectively) (Keplinger and Suissa 1968). Rats exposed to these concentrations experienced eye irritation, slightly labored breathing and very mild to mild diffuse congestion of the lungs. No-effect levels and exposure times were 88 ppm for 5 minutes, 49 ppm for 15 minutes, 35 ppm for 30-minutes, and 28 ppm for 60 minutes.

Groups of 10 Osborne-Mendel rats were treated with single and repeated exposures of fluorine (Keplinger 1969). Single exposures occurred for 5 minutes at concentrations of 85-150 ppm and 256-450 ppm, for 30 minutes at 46-68 ppm, and for 60 minutes at 45-75 ppm and 88-170 ppm. The animals were sacrificed immediately after exposure or at 7, 14, 21, or 45 days after the last exposure; however, the day of sacrifice for each test was not reported. Gross pathology results were not well described, and results of each individual test were not reported; those results that were reported are summarized in Table 4. Single exposures for 5 minutes at 85-150 ppm induced very mild lung congestion and some kidney changes, but no liver lesions. At the higher concentrations, 256-450 ppm, moderate diffuse congestion of the lungs and gross damage (primarily discoloration) of the liver and kidneys occurred. Following exposure to 46-68 ppm for 30 minutes, the livers were grossly normal while the lungs and kidneys showed slight gross pathologic changes. Exposure for 60 minutes at the lower concentration range resulted in lung and kidney changes but no effect on the liver. At the higher concentration range, severe diffuse congestion and hemorrhages of the lungs were observed. Both the kidneys and livers showed gross changes.

Keplinger (1969) also reported on repeated exposure. Lung, kidney and liver effects in rats exposed four times at daily to weekly intervals to various concentrations were compared with effects following a single treatment at the same concentration. Effects on the lungs (congestion, hemorrhage), kidneys, and liver were greater following the single exposure than following the repeated weekly exposures. For example, four repeated exposures to 30 ppm for

60 minutes every other day produced lesser effects than a single exposure to 30 ppm for 60 minutes; sacrifice occurred immediately after the last or single exposure (Keplinger 1969).

3.2.3. Mice

Sublethal effects of inhalation exposure to fluorine were assessed in Swiss-Webster mice exposed to concentrations equal to 78% of the 5-minute LC_{50} (467 ppm) and 50% of the 5-minute, 15-minute, 30-minute, and 1-hour LC_{50} values (300, 188, 113, and 75 ppm, respectively) (Keplinger and Suissa 1968). A few additional tests were carried out at concentrations between the LC_{50} and 50% of the LC_{50} (Keplinger 1969). Very few signs of intoxication were observed immediately after exposure. Mice exposed to 467 ppm for 5 minutes experienced marked irritation of the eyes and respiratory tract immediately after exposure and labored breathing and lethargy were observed several hours later. At sacrifice there was severe diffuse congestion of the lungs. At concentrations equal to 50% of the 5-minute, 15-minute, and 60-minute LC_{50} values, mice showed moderate to severe diffuse congestion of the lungs.

In mice exposed to sublethal concentrations (specific concentrations not stated) there was some evidence of gross damage to the lungs, liver, and kidneys (Keplinger and Suissa 1968). Histological examination of the lungs revealed massive hemorrhages into the alveolar spaces and coagulation necrosis of alveoli with peribronchial lymphocytic proliferation. After 7 days there was proliferation of septal cells, macrophages and lymphocytes. Beginning at 7 days post exposure, livers showed coagulation necrosis, periportal hemorrhages and diffuse cloudy swelling. Focal areas of coagulation necrosis appeared in the cortex of the kidney and focal areas of lymphocytic infiltration appeared throughout the cortex and medulla. Concentrations that caused no effects in the lungs did not cause effects in the liver or kidneys. Damage occurred in both the lung and kidney at the same concentration; liver changes occurred at higher concentrations. Although not specifically stated for each species, some or all of these same effects occurred in other species to the same or a lesser degree.

Mild effects were observed in mice at 174 ppm (5 minutes), 87 ppm (15 minutes), 67 ppm (30 minutes), and 50 ppm (60 minutes) (Keplinger and Suissa 1968). No-effect concentrations for organ pathology were 79 ppm for 5 minutes, 65 ppm for 15 minutes, 51 ppm for 30 minutes, and 30 ppm for 60 minutes. Four repeated exposures such as 30 ppm for 60 minutes every other day produced lesser effects than a single exposure of the same magnitude; sacrifice occurred immediately after the last or single exposure (Keplinger 1969).

3.2.4. Guinea pigs

Disabling, irreversible effects were not observed in New England guinea pigs exposed to concentrations lower than the LC_{50} values (Keplinger and Suissa 1968). In guinea pigs exposed to 50% of the 15-minute LC_{50} (198 ppm), signs of eye and respiratory irritation and labored breathing and gross lung changes of mild diffuse congestion were present. At exposures to concentrations of 100 and 70 ppm for 5 minutes, mild effects were occasionally observed. For the 60-minute exposures, eye and respiratory irritation and mild diffuse congestion of the lung were observed at 135 ppm (79% of the 60-minute LC_{50}) and no effects were observed at 73 ppm (43% of the 60-minute LC_{50}).

3.2.5. Rabbits

Eye and respiratory irritation and moderate diffuse congestion of the lungs were observed in New Zealand rabbits exposed to 410 ppm for 5 minutes (50% of the 5-minute LC_{50}) (Keplinger and Suissa 1968). Effects in rabbits at 16% of the 5-minute LC_{50} (134 ppm) and 50% of the 30-minute LC_{50} (135 ppm) were slight to mild (Keplinger and Suissa 1968). In short-term, repeated exposures, rabbits administered fluorine at a concentration of 0.5 ppm for up to 35 days (presumably 5 hours/day) showed little or no lung damage (Stokinger 1949).

3.3. Developmental/Reproductive Toxicity

No studies addressing developmental or reproductive effects following acute inhalation exposure to fluorine were located.

3.4. Genotoxicity

No data on inhalation exposures were located in the available literature. Genotoxicity studies were conducted with sodium fluoride or potassium fluoride. Negative results were found for *Salmonella typhimurium* TA100, TA1535, TA1537, and TA98 with or without metabolic activation, and positive results were found in the mouse lymphoma (with and without activation), sister chromatid exchange (with and without activation), and chromosome aberration tests (without activation) (NTP 1990), but generally at doses that produced cellular toxicity (ATSDR 2003).

3.5. Chronic Toxicity/Carcinogenicity

No carcinogenicity studies using acute or longer-term inhalation exposure were located. Because inhaled fluorine would exert its systemic effects as fluoride ion, oral studies of fluoride administration may be relevant. A chronic oral carcinogenicity study in which sodium fluoride was administered to male and female rats and mice in the drinking water resulted in equivocal evidence of bone cancer in male rats, but not in female rats or mice of either gender (NTP 1990). The cancer was a rare bone osteosarcoma. Another chronic oral study, with sodium fluoride administered in the feed found no evidence of cancer in male or female rats (Maurer et al. 1990).

3.6. Summary

LC_{50} concentrations for the mouse, rat, guinea pig, and rabbit from the study of Keplinger and Suissa (1968) are summarized in Table 5 and graphed in Figure 1. With the exception of the 5-minute LC_{50} for the rabbit, the LC_{50} values for all four species at the different exposure times were not statistically significantly different. Additionally, a 7-hour LC_{54} value of 100 ppm for the rat was available (Eriksen 1945; Stokinger 1949).

No data on acute inhalation and developmental toxicity were located. Genotoxicity was observed only at concentrations that were toxic to cells (ATSDR 2003). Chronic/carcinogenicity studies with oral administration of sodium fluoride resulted in equivocal evidence of cancer in one study (NTP 1990) and no evidence of cancer in a second study (Maurer et al. 1990).

TABLE 5. Summary of LC_{50} Data in Animals (ppm)				
Exposure Time	**Rat**	**Mouse**	**Guinea pig**	**Rabbit**
5 min	700	600	--	820
15 min	390	375	395	--
30 min	270	225	--	270
60 min	185	150	170	--

Source: Keplinger and Suissa (1968).

A dash ( ) indicates no data.

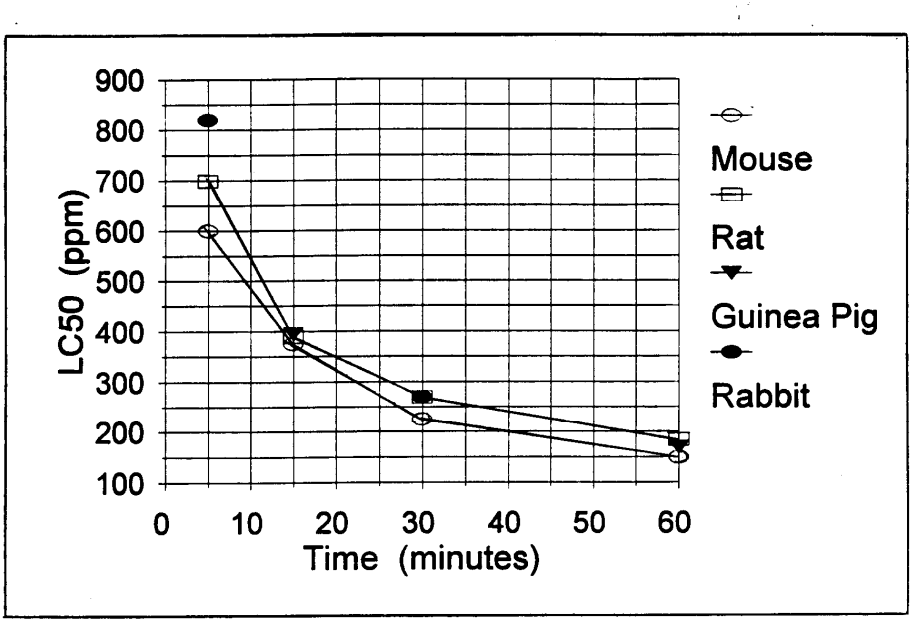

Figure 1. LC_{50} Values for four species of animals. The continuous lines represent values for the mouse and rat.
Source: Keplinger and Suissa (1968).

The only experimental data available for longer-term exposures was the 7-hour exposure of rats, mice, guinea pigs and rabbits to 100 ppm which resulted in an over-all mortality of 60% (Eriksen 1945; Stokinger 1949). At this exposure concentration and duration, the mouse and rabbit were the most sensitive species as indicated by high mortality, the rat was intermediate in sensitivity, and the guinea pig was the least sensitive species with no mortality.

Lowest values for disabling, irreversible effects; nondisabling, reversible effects; and no-effect concentrations for various exposure periods for each species are summarized in Table 6. In many cases, the listed concentration is the only tested concentration.

TABLE 6. Summary of Nonlethal Effects in Animals[a]				
Species	Exposure Time	Disabling Effects (ppm)	Nondisabling Effects (ppm)	No Effect (ppm)
Dog	5 min	--	--	--
	15 min	--	93	--
	30 min	--	--	--
	60 min	93	68	38
Rat	5 min	325	150	88
	15 min	195	98	49
	30 min	140	70	35
	60 min	140	47	28
Mouse	5 min	300	130	79
	15 min	188	87	65
	30 min	--	64, 67	32
	60 min	75	30	15
Guinea pig	5 min	--	--	--
	15 min	--	198	70
	30 min	--	--	--
	60 min	--	135	73
Rabbit	5 min	410	134	51
	15 min	--	--	--
	30 min	--	135	32
	60 min	--	--	--

[a]Effects include both irritation and organ lesions.
A dash (--) indicates no data.
Source: Keplinger and Suissa 1968.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Pharmacokinetic data from acute exposures were not available. Metabolic/kinetic considerations are not relevant regarding the determination of AEGL values as animals die of acute respiratory failure. Fluorine is hygroscopic and will react with the moist mucus membranes of the respiratory passages.

Following inhalation, fluorine may be absorbed by the lungs, particularly following the formation of hydrofluoric acid by reaction with moisture in the lungs. Fluoride from the circulating blood is deposited in the bone where it substitutes for the hydroxyl group of hydroxyapatite, the principal mineral component of bone. Renal excretion of fluoride is rapid; accumulation in the kidney occurs as fluoride is concentrated in the urine for elimination (Teitelbaum 2001).

4.2. Mechanism of Toxicity

Although fluorine reacts with water vapor in the moist respiratory passages, some fluorine persists in saturated water vapor for periods up to one hour (Slabey and Fletcher 1958). Therefore, it is likely that some of the inhaled fluorine will persist in the elemental form in the saturated air of the respiratory tract and will be carried into the lungs. The available studies show that damage to the respiratory tract, particularly the lung (edema, emphysema, and

hemorrhage), is the major pathology associated with acute exposure to fluorine (Eriksen 1945; Stokinger 1949; Keplinger and Suissa 1968; Keplinger 1969). Fluorine is characterized as a severe irritant to the eyes, mucous membranes, skin, and lungs (ACGIH 2004; NRC 1984). Serious systemic effects are unlikely to occur from an acute exposure. In the studies summarized in Table 4, the eye and tissues of the respiratory tract sustain the impact of an acute exposure. Therefore, the concentration of fluorine in the inhaled air and not the absorbed dose is the primary determinant of effects.

4.3. Structure-Activity Relationships

The combined human and animal data on fluorine are sufficient for derivation of inhalation exposure guidelines and the use of structure-activity comparisons is not necessary. Like hydrogen chloride (HCl) and chlorine (Cl_2), fluorine is an irritant to the eyes, skin, and respiratory tract. When compared with mortality data for HCl and chlorine (Cl_2), fluorine is more toxic than HCl and slightly more toxic than Cl_2 to laboratory rodents. Mortality data indicate that HF is more toxic than HCl but less toxic than F_2 to laboratory rodents (Wohlslagel et al. 1976; Teitelbaum 2001; ATSDR 2003: NRC 2004). Kusewitt et al. (1989) exposed Fischer 344 rats to hydrogen halides at concentrations of 100 to 1000 ppm for 30 minutes. Tissue injury was confined to the nasal region with relative toxicities of HF>HCl$HBr.

Penetration of any chemical to the lungs depends on water solubility. The more water soluble halides are scrubbed in the upper respiratory passages, and there is less penetration to the bronchioles and lungs. Fluorine decomposes water, forming HF, OF_2, hydrogen peroxide, oxygen, and ozone (O'Neil et al. 2001). The same reaction is predicted to occur in the moist respiratory passages. However, some unreacted fluorine will penetrate to the lungs. The water solubility of chlorine is 0.092 mol/L (25EC) , and the water solubility of bromine is 0.214 mol/L (20EC). For the endpoint of lethality, the order of water solubility is also the order of toxicity, i.e., fluorine is poorly scrubbed and therefore more easily penetrates to the lungs, resulting in lower LC_{50} values than for the other halogens. For example, the 1-hour LC_{50} values for chlorine in the rat range from 293-455 ppm (NRC 2004), whereas, the value for fluorine in the Keplinger and Suissa 1968 study is 185 ppm. Both chlorine and bromine are more readily scrubbed in the upper respiratory tract than is fluorine.

4.4. Concentration-Exposure Duration Relationship

When data are lacking for desired exposure times, scaling across time may be based on the relationship between acute toxicity (concentration) and exposure duration (ten Berge et al. 1986). The only available data for scaling across time are LC_{50} data for the rat, mouse, and guinea pig for 5, 15, 30, and 60-minute exposure durations. These data show that the association between concentration and exposure duration is a logarithmic one and the equations derived from the empirical data by regression analysis are expressed as $C^n \times t = k$ (where C = concentration, t = time in minutes, and k is a constant). For the three species the equations derived from the LC_{50} data are:

$C^{1.87} \times t = 1.05 \times 10^6$ ppmAminute (rat)
$C^{1.77} \times t = 4.45 \times 10^5$ ppmAminute (mouse)
$C^{1.64} \times t = 2.79 \times 10^5$ ppmAminute (guinea pig)

Therefore, the relationship between concentration and time in approximately $C^2 \times t = k$. Appendix A contains a graph of this relationship for the mouse data.

4.5. Other Relevant Information

4.5.1. Susceptible Populations

No data on susceptible populations were located. Fluorine is highly irritating and corrosive to the tissues of the respiratory tract. The direct action of fluorine on the respiratory tract is not expected to vary greatly among most individuals. Although no data on fluorine exposures and asthmatics were located, studies with chlorine indicate that, compared with the general population, the respiratory tract of some asthmatics may be very reactive to the presence of irritant gases (NRC 2004). Machle and Evans (1940) reviewed several monitoring studies in which undefined exposures to fluorine in industry resulted in increased asthmatic attack frequency compared to that in the non-exposed population.

4.5.2. Species Variability

A comparison of the animal and human data indicates that humans may be more sensitive to the irritant effects of fluorine than animals in that experimental animals suffered no gross effects at concentrations that humans found intolerable. For example, a concentration of 73 ppm for 1 hour was a no-effect concentration for the guinea pig, but humans could not inhale 78 ppm for a short time without coughing.

Rats and rabbits exposed to 10,000 ppm of fluorine exhibited similar pulmonary damage; however, pulmonary hemorrhage was extensive in the rabbit whereas it was absent or extremely slight in the rat (Eriksen 1945; Stokinger 1949). At concentrations of 200 ppm and above, mortality rates were similar for rats, mice, rabbits, and guinea pigs for the different time periods. Guinea pigs succumbed more rapidly than the other three species at the three highest exposure levels (10,000, 1000, and 500 ppm), but showed less mortality at the 200 ppm level and no mortality at the 100 ppm level. These data, although slightly conflicting at times, do not indicate great species variability in response to fluorine exposures.

In another study, the 5-, 15-, 30-, and 60-minute LC_{50} values for the rat, mouse, rabbit, and guinea pig were remarkably similar with only slightly lower values for the mouse compared to the other species (Keplinger and Suissa 1968). In all cases, death resulted from acute pulmonary edema and consequent respiratory failure. The similarity in LC_{50} values for each time period suggests similar species sensitivity.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

A number of authors report 10 ppm as a concentration that caused either no discomfort or sensory irritation (Keplinger and Suissa 1968; Belles 1965). A higher level of 25 ppm caused eye irritation during a 5-minute exposure (Keplinger and Suissa 1968), sore throat and chest pains that lasted for 6 hours (duration of exposure not specified but presumed short) (Rickey 1959), and eye and nasal irritation after three breaths (Belles 1965). Humans were also exposed to 10 ppm for 3 to 5 minutes every 15 minutes over a two- to three-hour period with only slight irritation to the eyes and skin (Keplinger and Suissa 1968).

5.2. Summary of Animal Data Relevant to AEGL-1

The animal data indicated that at 25% of the LC_{50}, there were mild signs of intoxication characterized by slight labored breathing and closed eyes (Keplinger and Suissa 1968). Below 25% of the LC_{50} there were no gross signs of lung pathology. Using the data of Keplinger and Suissa (1968) and Keplinger (1969), Ricca (1970) estimated the no-effect concentration with respect to lung, liver, and kidney pathology (based on C x t values) at 15% of the rat LC_{50} concentration. For the 1-hour exposure, this concentration would be 28 ppm.

However, absence of apparent effects and gross signs of intoxication does not insure that slight irritation or discomfort did not take place. No-effect concentrations are listed in Table 6. No-effect concentrations for the rat are 35 ppm for 30 minutes and 28 ppm for 60 minutes. For the mouse, the 30- and 60-minute no-effect concentrations are 32 ppm and 15 ppm, respectively; the 60-minute no-effect concentrations for the dog and guinea pig are 39 and 73 ppm, respectively. For all species, the 30-minute no-effect concentrations range from 32 to 35 ppm and the 60-minute no-effect concentrations range from 15 to 73 ppm. These values do not necessarily indicate the relative sensitivity of the species but, rather, reflect the experimental concentrations selected by the researchers.

5.3. Derivation of AEGL-1

Because human data for irritant effects are available, they should be used to derive the AEGL-1. The data of Keplinger and Suissa (1968) are the most comprehensive for humans exposed to 10 ppm. The 10 ppm concentration for 15 minutes was reported as a no-effect level for eye and nasal irritation but can be considered the threshold for notable discomfort as the next highest concentration tested, 25 ppm, produced slight to moderate discomfort. The 15-minute time was the longest exposure duration for which no irritation was reported. An intraspecies uncertainty factor of 3 was applied to this NOAEL value because the contact irritation from the highly corrosive fluorine is not expected to vary greatly among individuals, including susceptible individuals (NRC 2001). Although no data on asthmatics were found, the uncertainty factor of 3 is considered adequate to protect this sensitive subpopulation because the value is a NOAEL and because shorter-term, repeated exposures produced only slight irritation in healthy individuals. The value is supported by a second study in which volunteers “tolerated” exposure to 10 ppm for an undefined period of time (Belles 1965).

The clinical and experimental data base for human and animal exposures is limited to a single study (Keplinger and Suissa 1968). Other than the review of fluorine industrial exposures by Machle and Evans (1940) in which asthma attacks occurred more frequently in the industry than in non-exposed populations, no data on sensitive populations were found. A modifying factor of 2 was applied based on this limited data base. The resulting value of 1.7 ppm (10 ppm/6) was used across all AEGL-1 exposure durations (Table 7; Appendix B) because at mildly irritating concentrations there is accommodation to irritating gases. This value is supported by limited workplace monitoring data: workers exposed to fluorine at average yearly concentrations up to 1.2 ppm (range, 0.0-17 ppm) over a four-year period reported fewer incidences of respiratory complaints or diseases than a similar group of nonexposed workers (Lyon 1962). The workers are assumed to encompass a small range of sensitivity; the additional intraspecies uncertainty factor of 3 was considered sufficient to protect sensitive individuals.

TABLE 7. AEGL-1 Values for Fluorine				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
1.7 ppm (2.6 mg/m^3)	1.7 ppm (2.6 mg/m^3)	1.7 ppm (2.6 mg/m^3)	1.7 ppm (2.6 mg/m^3)	1.7 ppm (2.6 mg/m^3)

A category plot of the animal and human data in relation to the AEGL values can be found in Appendix C.

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

Irritant effects were noted in human volunteers at concentrations of 25 ppm for 5 minutes and 50 ppm for 3 minutes. Irritant effects at these concentrations were described as slight and are below the discomfort described by the AEGL-2 definition. The concentration of 67 ppm for 1 minute was described as irritating to the eyes and nose but not unbearable. This description is similar to that of the AEGL-2, but the exposure period is extremely short.

6.2. Summary of Animal Data Relevant to AEGL-2

In the animal studies, Keplinger and Suissa (1968) characterized the symptoms of exposure equivalent to approximately 25% of the LC_{50} as mild with slightly labored breathing, closed eyes, and mild to very mild lung congestion. For the respective species, 30-minute concentrations corresponding to 20-25% of the LC_{50} were 70 ppm (rat), 67 ppm (mouse), and 71 ppm (rabbit). One-hour concentrations corresponding to 20-43% of the LC_{50} were 47 ppm (rat), 30 ppm (mouse), and 73 ppm (no-effect concentration for guinea pig); these data are summarized in Table 6.

6.3. Derivation of AEGL-2

Mild lung congestion was chosen as the threshold for irreversible or other serious, long-lasting effects as defined by the AEGL-2. The mouse was chosen as the most sensitive species although the experimental results for respective exposure periods for the tested species are very similar. The single data set (Keplinger and Suissa 1968) was extensive, being based on five species and four exposure durations. The mildest effects noted in the Keplinger and Suissa (1968) study were very mild or mild diffuse congestion which were observed at approximately 25% (20-43%) of the LC_{50} values. The rapid change in effects as the LC_{50} is successively halved indicates the steepness of the dose-response curve for fluorine.

The mouse 30-minute and 1-hour values which caused very mild lung congestion were chosen for calculation of the AEGL-2 values. These concentrations are 67 ppm (30% of the 30-minute LC_{50}) and 30 ppm (20% of the 60-minute LC_{50}), respectively. An interspecies uncertainty factor of 1, an intraspecies uncertainty factor of 3, and a modifying factor of 2 were then applied to these numbers to derive the AEGL-2 (see discussion of uncertainty factors for AEGL-3). Extrapolation across time was based on the equation for the mouse, $C^{1.77} \times t = k$. The 4- and 8- hour values were scaled from the 1-hour value (see Appendix B for calculations). The values are listed in Table 8. The 8-hour-AEGL-2 value was set equal to the 4-hour value

because at low concentrations the hygroscopic fluorine would react with and/or be scrubbed by the nasal passages, and because at mildly irritating concentrations, adaptation to sensory irritation occurs.

TABLE 8. AEGL-2 Values for Fluorine				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
20 ppm (31 mg/m^3)	11 ppm (17 mg/m^3)	5.0 ppm (7.8 mg/m^3)	2.3 ppm (3.6 mg/m^3)	2.3 ppm (3.6 mg/m^3)

Although human exposure for durations longer than 1 minute were to concentrations below the definition of the AEGL-2, a comparison of the human data with the derived values can be made. Extrapolating the 3-minute exposure to 50 ppm from the data of Keplinger and Suissa (1968) to a 30-minute time period results in a value of 13.6 ppm. The effects during this exposure, eye irritation (not otherwise specified) and slight nose irritation, are below the definition of the AEGL-2.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No information on irreversible or life-threatening effects caused by fluorine in humans was located. A concentration of 50 ppm was characterized as irritating and concentrations of 67-100 ppm were "very irritating and became uncomfortable after a few seconds."

7.2. Summary of Animal Data Relevant to AEGL-3

In the animal studies, Keplinger and Suissa (1968) characterized the symptoms of exposure equivalent to 50% of the LC_{50} values as "dyspnea, lethargy, red nose, and swollen eyes." No deaths occurred in any species (dog, rat, mouse, guinea pig, rabbit) at approximately 50% of the respective LC_{50} values. All species tested at 50% of the LC_{50} survived for up to 45 days post exposure. Effects ranged from disabling, characterized by respiratory irritation and labored breathing with severe diffuse lung congestion (mouse, 50% of the 1-hour LC_{50}), to practically non-disabling, characterized by no eye or nose irritation and very mild diffuse lung congestion (guinea pig, 43% of the 1-hour LC_{50}). At 50% of the 15-minute LC_{50}, guinea pigs showed signs of respiratory irritation and labored breathing and gross changes in the lungs of mild diffuse congestion. Mice were tested at 50, 34, 20, and 10% of the LC_{50} for a 60-minute exposure period. At a concentration equal to 50% of the 60-minute LC_{50}, the mouse showed signs of irritation and labored breathing and severe diffuse congestion of the lungs. At concentrations equal to 34 and 20% of the 60-minute LC_{50}, effects in the mouse were mild and very mild diffuse congestion, respectively, whereas the guinea pig, tested at 43% of its 60-minute LC_{50} suffered no effects. The dog was tested at a concentration closer to one-third (93 ppm) rather than one-half of the 1-hour LC_{50} concentration for the other species; at this concentration effects on the lungs were slight and would be more likely defined as an AEGL-2 level of effect. From the data involving effects at concentrations lower than the LC_{50} values for the various time periods, the guinea pig appears to be the least sensitive species and the mouse is the most sensitive species. The only experimental data available for longer term exposures was the 7-hour exposure of rats, mice, guinea pigs and rabbits to 100 ppm which resulted in an over-all mortality of 60% (Eriksen 1945; Stokinger 1949). The extrapolated data of Keplinger and

Suissa (1968), 7-hour LC_{50} values of 65 and 50 ppm for the rat and mouse, respectively, yield more conservative concentrations.

7.3. Derivation of AEGL-3

The LC_{50} values for the rat and mouse are very close for the 15, 30, and 60 minute time periods (Keplinger and Suissa 1968). At 15 and 60 minutes, the mouse, rat, and guinea pig LC_{50} values are almost identical (Table 5). At 30 minutes the mouse, rat, and rabbit LC_{50} values are very close. The strong concordance of the LC_{50} values between four animal species at three time points presents a strong case for the conclusion that lethality is a function of the concentration of fluorine in the air. Therefore, the exposure concentration equals the dose for fluorine and there is no need for scaling factors among species. Keplinger and Suissa (1968) demonstrated that at 50% of the LC_{50} there were no deaths in five tested species in a total of 13 tests conducted over a 5- to 60-minute exposure duration. Therefore, 50% of the LC_{50} concentration was chosen as the NOEL for "life threatening effects." The mouse was chosen as the most sensitive species although all of the LC_{50} values were very similar. The 60-minute value of 75 ppm was used as the basis for the AEGL-3.

Fluorine is a contact-site, direct-acting toxicant; there is no metabolic or pharmacokinetic component to fluorine-induced effects and there is likely to be little difference between species or among individuals in the response of biological tissues to fluorine exposure. The fact that the LC_{50} values for four species were essentially identical, and the mechanism of action is direct chemical (corrosive) destruction of lung tissue would argue for the use of an uncertainty factor of 1 when extrapolating from animals to man. However, the data used to develop the AEGL-3 were obtained primarily from one laboratory and not confirmed elsewhere. Therefore, a modifying factor of 2 is used for this uncertainty. A factor of 3 is added to account for variability in human susceptibility (fluorine is a highly reactive, corrosive gas whose effect on the respiratory tissues is not expected to differ greatly among individuals). The combined uncertainty/ modifying factor is 6. Concentrations were scaled across time using the $C^{1.77} \times t = k$ relationship. Scaling from the 1-hour experimental value to the 8-hour exposure duration was considered realistic based on the similarity of extrapolated LC_{50} values from the Keplinger and Suissa (1968) study and the 7-hour experimental values from the Eriksen (1945) and Stokinger (1949) study. The 8-hour value was set equal to the 4-hour value as was done for the AEGL-2. Values are summarized in Table 9 and calculations are in Appendix B.

TABLE 9. AEGL-3 Values for Fluorine

10-min	30-min	1-h	4-h	8-h
36 ppm (56 mg/m^3)	19 ppm (29 mg/m^3)	13 ppm (20 mg/m^3)	5.7 ppm (8.8 mg/m^3)	5.7 ppm (8.8 mg/m^3)

8. SUMMARY OF PROPOSED AEGLS

8.1. AEGL Values and Toxicity Endpoints

In summary, the AEGL values for various levels of effects and various time periods were derived using the following methods. The AEGL-1 was based on a study with human volunteers in which a concentration of 10 ppm administered for 15 minutes produced no irritation of the eyes, nose, or respiratory tract. This value was divided by 3 to account for differences in human

sensitivity. Although no data on asthmatics, a potentially susceptible populations were found, the fact that healthy humans have "tolerated" short-term exposures to 17 ppm indicates that the uncertainty factor of 3 is sufficient. A modifying factor of 2 was applied based on a limited data base. Because accommodation to the irritant effects of irritant gases occurs at mildly irritating concentrations, the derived value of 1.7 ppm was applied across all AEGL-1 time intervals.

In the absence of relevant human data, animal data were used to derive the AEGL-2 and AEGL-3 values. AEGL-2 values were derived based on concentrations equal to 25% of the LC_{50} values from a study with the most sensitive species, the mouse. These concentrations, 67 and 30 ppm for 30- and 60 minute exposures, respectively, produced only very mild lung congestion. An uncertainty factor of 3 for differences in human sensitivity and a modifying factor of 2 for the use of a single data set were then applied to these numbers. Extrapolation across time was based on the regression equation for LC_{50} values and exposure times in the mouse, $C^{1.77} \times t = k$.

The AEGL-3 values were based on data using the laboratory mouse in which severe effects but no deaths were noted at 50% of the 30- and 60-minute LC_{50} values (113 and 75 ppm, respectively). A concentration equal to 50% of the 60-minute LC_{50} was selected from the mouse studies and scaled to other exposure times using the equation $C^{1.77} \times t = k$. An uncertainty factor of 3 for differences in human sensitivity and a modifying factor of 2 for the fact that the data set came from one laboratory and was not confirmed elsewhere were applied.

The AEGLs are summarized in Table 10. A summary of the derivations is contained in Appendix D.

TABLE 10. Summary of AEGL Values

Classification	Exposure Duration				
	10-min	**30-min**	**1-h**	**4-h**	**8-h**
AEGL-1[a] (Nondisabling)	1.7 ppm (2.6 mg/m^3)	1.7 ppm (2.6 mg/m^3)	1.7 ppm (2.6 mg/m^3)	1.7 ppm (2.6 mg/m^3)	1.7 ppm 2.6 mg/m^3)
AEGL-2[b] (Disabling)	20 ppm (31 mg/m^3)	11 ppm (17 mg/m^3)	5.0 ppm (7.8 mg/m^3)	2.3 ppm (3.6 mg/m^3)	2.3 ppm (3.6 mg/m^3)
AEGL-3 (Lethal)	36 ppm (56 mg/m^3)	19 ppm (29 mg/m^3)	13 ppm (20 mg/m^3)	5.7 ppm (8.8 mg/m^3)	5.7 ppm (8.8 mg/m^3)

[a] AEGL-1 values held constant across time because of accommodation to mildly irritating concentrations of irritant gases.
[b] 30-minute and 1-hour AEGL-2 values are based on separate data points.

8.2. Comparison with Other Standards and Guidelines

Standards and guidance levels for workplace and community exposures are listed in Table 11. The AEGL values are very close to other guidelines for emergency exposures. The NIOSH IDLH 30-minute value refers to respirator use, but is slightly higher (25 ppm) than the 30-minute AEGL-3 of 19 ppm. The NIOSH IDLH is based on the observation of Rickey (1959) that two men were able to tolerate 25 ppm very briefly but both developed sore throats and chest pains that lasted 6 hours; 50 ppm could not be tolerated. The definitions of the preliminary ERPGs correspond to the three AEGLs. The ERPG 1-hour values were recently changed from 2, 7.5, and 10 ppm to 0.5, 5, and 20 ppm, reasonably close to the AEGL values. Documentation for the values was not given in this source. The NRC Emergency Exposure Guidance Levels

(EEGLs) are for occupational exposures and not the general public. The 30- and 60-minute EEGLs are 10 and 7.5 ppm whereas the 30- and 60-minute AEGL-2 values are 11 and 5 ppm. The EEGL guidelines are based on the human and animal data of Keplinger and Suissa (1968).

Although the populations are not comparable, the ACGIH TLV-TWA and STEL of 1 and 2 ppm, respectively, are similar to the AEGL-1 value of 1.7 ppm. The ACGIH TLV-TWA guideline is based on the lack of significant medical findings in workers exposed to fluorine for 7 years (Lyon 1962) coupled with evidence of tolerance development in animals (Keplinger 1969). The ACGIH TLV-STEL is based on the human study in which exposures to 10 ppm, repeated for 3 to 5 minutes every 15 minutes for 2-3 hours, produced only slight irritation to the eyes and skin (Keplinger and Suissa 1968). The OSHA PEL-TWA is also based on the Lyon (1962) study; however, OSHA and NIOSH believed that the Lyon study did not involve 61 workers continually exposed but instead was a compilation of data on workers who may have had some short-term exposure to fluorine. Thus, their TWA is 10 times lower than that of ACGIH. Neither NIOSH or OSHA have promulgated short-term exposure limits (STELs). The German MAK and Dutch MAC peak limits are both 0.2 ppm.

TABLE 11. Extant Standards and Guidelines for Fluorine

Guideline	Exposure Duration				
	10 min	**30 min**	**1 h**	**4 h**	**8 h**
AEGL-1	1.7 ppm	1.7 ppm	1.7 ppm	1.7 ppm	1.7 ppm
AEGL-2	20 ppm	11 ppm	5.0 ppm	2.3 ppm	2.3 ppm
AEGL-3	36 ppm	19 ppm	13 ppm	5.7 ppm	5.7 ppm
ERPG-1 (AIHA)[a]			0.5 ppm		
ERPG-2 (AIHA)			5 ppm		
ERPG-3 (AIHA)			20 ppm		
EEGL (NRC)[b]	15 ppm	10 ppm	7.5 ppm		
IDLH (NIOSH)[c]		25 ppm			
REL-TWA (NIOSH)[d]					0.1 ppm
PEL-TWA (OSHA)[e]					0.1 ppm
TLV-TWA (ACGIH)[f]					1 ppm
TLV-STEL (ACGIH)[g]					2 ppm
MAK (Germany)[h]					0.1 ppm
MAK Peak Limit (Germany)[i]					0.2 ppm
MAC Peak Limit (The Netherlands)[j]					0.2 ppm

[a]**ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association** (AIHA 2004)
The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.
The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action.
The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing life-threatening health effects.

[b]**EEGL (Emergency Exposure Guidance Levels, National Research Council** (NRC 1984)
The EEGL is the concentration of contaminants that can cause discomfort or other evidence of irritation or intoxication in or around the workplace, but avoids death, other severe acute effects and long-term or chronic injury.

[c]**IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health)** (NIOSH 2004a) represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects.

[d]**NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average)** (NIOSH 2004b) is defined analogous to the ACGIH-TLV-TWA.

[e]**OSHA PEL-TWA (Occupational Health and Safety Administration, Permissible Exposure Limits - Time Weighted Average)** (NIOSH 2004b) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week.

[f]**ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average)** (ACGIH 2004) is the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[g]**ACGIH TLV-STEL (Threshold Limit Value - Short Term Exposure Limit)** (ACGIH 2004) is defined as a 15-minute TWA exposure which should not be exceeded at any time during the workday even if the 8-hour TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 minutes and should not occur more than 4 times per day. There should be at least 60 minutes between successive exposures in this range.

[h]**MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration])** (Deutsche Forschungsgemeinschaft [German Research Association] 2002) is defined analogous to the ACGIH-TLV-TWA.

[i]**MAK Spitzenbegrenzung (Peak Limit [give category])** (German Research Association 2002) constitutes the maximum average concentration to which workers can be exposed for a period up to 30 minutes with no more than 2 exposure periods per work shift; total exposure may not exceed 8-hour MAK.

[j]**MAC (Maximaal Aanvaarde Concentratie [Maximal Accepted Concentration])** (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000) is defined analogous to the ACGIH-TLV-TWA.

8.3. Data Adequacy and Research Needs

Data from human studies are sparse and used healthy human subjects; exposures were usually short-term, with some exposure durations not stated. The study by Keplinger and Suissa (1968) used several short exposure durations and concentrations were measured. Data from animal studies used five species and encompassed a wide range of exposure concentrations and exposure durations, but none of the durations was for longer than one hour for less than lethal effects. The animal studies were undertaken 27-47 years ago and analytical techniques have improved since then. The data base for human studies is inadequate (except for the AEGL-1) and the data base for animal studies is adequate, at least for 30- and 60-minute exposures.

Although data from one study could be used to estimate the concentration-exposure duration relationships for several animal species ($C^n \times t = k$), the longest exposure duration was only 1 hour. The study of Eriksen (1945) and Stokinger (1949), although flawed due to difficulty in monitoring the test concentrations, tend to support the extrapolation to longer exposure times. Their single data point for the rat, 54% mortality at a concentration of 100 ppm for 7 hours, when extrapolated to a 1-hour exposure gives an approximate LC_{50} of 300 ppm (the actual concentration is probably lower due to chamber losses [Ricca 1970]). This value is within a factor of 2 of the 1-hour LC_{50} for the rat of 187 ppm in the Keplinger and Suissa study.

The total body of data on the sublethal and lethal effects of fluorine is reasonably consistent. The mechanism of action is understood. Although most of the experimental exposures were of short duration, at least one additional experimental value is consistent with the derived time-scaling relationship. Application of an intraspecies uncertainty factor of 3 to the human data, an interspecies uncertainty factor of 1 to the animal data, and a modifying factor of 2 to reasonably consistent but limited human and animal data is appropriate to insure the safety of the values.

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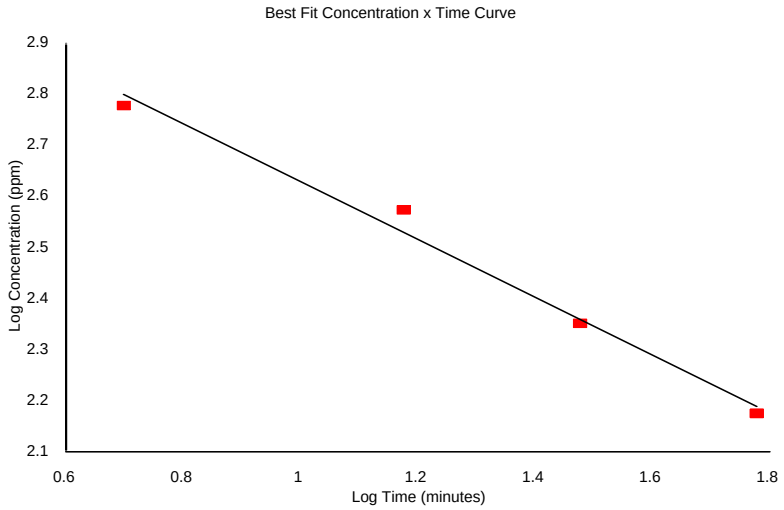
APPENDIX A: Time-Scaling Graph for Fluorine



Data (Keplinger and Suissa 1968; LC_{50} values for the mouse):

Time (minutes)	Concentration (ppm)	Log time	Log concentration
5	600	0.6990	2.7782
15	375	1.1761	2.5740
30	225	1.4771	1.3522
60	150	1.7782	2.1761

Regression Output:

Intercept	3.1958
Slope	-0.5658
R Squared	0.9872
Correlation	-0.9936
Degrees of Freedom	2
Observations	4

n = 1.77
k = 444989

APPENDIX B: Derivation of AEGL Values

Derivation of AEGL-1

Key study:	Keplinger and Suissa 1968
Toxicity endpoint:	No irritant effects in humans exposed to 10 ppm for 15 minutes
Scaling:	Not used; because accommodation to low concentrations of fluorine, the values were not time-scaled
Uncertainty factor:	3 for differences in human sensitivity (an uncertainty factor of 3 rather than 10 was used because 10 ppm for 15 minutes is a no-effect level; in addition, fluorine reacts chemically with the tissues of the respiratory tract and effects are unlikely to differ among individuals).
Modifying factor:	2 to account for a single data set
Calculation:	10 ppm/6 = 1.7 ppm

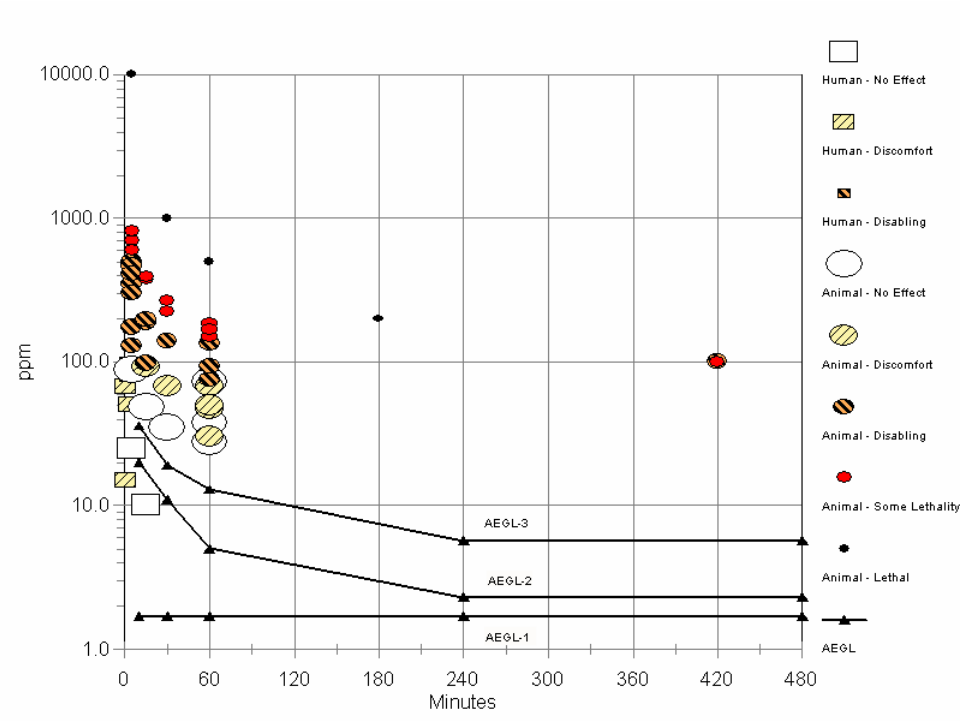
Derivation of AEGL-2

Key study:	Keplinger and Suissa 1968
Toxicity endpoint:	Very mild diffuse lung congestion in mice exposed to 67 ppm for 30 minutes and 30 ppm for 1 hour.
Scaling:	$C^{1.77}$ x t = k (ten Berge et al. 1986)
Uncertainty factors:	1 for interspecies differences (four species had similar LC_{50} values) 3 to account for differences in human sensitivity (the toxicity endpoint is a mild effect level and the toxic effect is due to a chemical reaction with biological tissue of the respiratory tract which is unlikely to be different among individuals)
Modifying factor:	2 to account for a single data set
Calculations:	$(67 \text{ ppm}/6)^{1.77}$ x 30 minutes = 2091 $\text{ppm}^{1.77}$ Aminutes $(30 \text{ ppm}/6)^{1.77}$ x 60 minutes = 1035.92 $\text{ppm}^{1.77}$Aminutes
10-min AEGL-2	$C^{1.77}$ x 10 minutes = 2091 $\text{ppm}^{1.77}$Aminutes C = 20 ppm
30-min AEGL-2	67 ppm/6 = 11 ppm
1-h AEGL-2	30 ppm/6 = 5 ppm
4-h AEGL-2	$C^{1.77}$ x 240 minutes = 1035.92 $\text{ppm}^{1.77}$Aminutes C = 2.3 ppm
8-h AEGL-2	Because of accommodation to low concentrations of irritant gases, the 8-hour value was set equal to the 4-hour value. C = 2.3 ppm

Derivation of AEGL-3

Key study:	Keplinger and Suissa 1968
Toxicity endpoint:	Severe diffuse lung congestion in mice exposed to 75 ppm for 1 hour
Scaling:	$C^{1.77} \times t = k$ (ten Berge et al. 1986)
Uncertainty factors:	1 for interspecies differences (four species had similar LC_{50} values) 3 to account for differences in human sensitivity (the toxic effect is due to a chemical reaction with biological tissue of the respiratory tract which is unlikely to be different among individuals)
Modifying factor:	2 to account for a single data set
Calculations:	$(75 \text{ ppm}/6)^{1.77} \times 60 \text{ minutes} = 5244.23 \text{ ppm}^{1.77}\text{minutes}$
10-min AEGL-3	$C^{1.77} \times 10 \text{ minutes} = 5244.23 \text{ ppm}^{1.77}\text{minutes}$ C = 36 ppm
30-min AEGL-3	$C^{1.77} \times 30 \text{ minutes} = 5244.23 \text{ ppm}^{1.77}\text{minutes}$ C = 19 ppm
60-min AEGL-3	75 ppm/6 = 13 ppm
4-h AEGL-3	$C^{1.77} \times 240 \text{ minutes} = 5244.23 \text{ ppm}^{1.77}\text{minutes}$ C = 5.7 ppm
8-h AEGL-3	Because of accommodation to low concentrations of irritant gases, the 8-hour value was set equal to the 4-hour value. C = 5.7 ppm

APPENDIX C: Category Graph of Toxicity Data and AEGL Values for Fluorine



APPENDIX D: Derivation Summary for Fluorine AEGLs

ACUTE EXPOSURE GUIDELINE LEVELS FOR FLUORINE (CAS Reg. No. 7782-41-4) DERIVATION SUMMARY

AEGL-1 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
1.7 ppm	**1.7 ppm**	**1.7 ppm**	**1.7 ppm**	**1.7 ppm**

Key Reference: Keplinger, , M.L. and L.W. Suissa. 1968. Toxicity of fluorine short-term inhalation. Am. Ind. Hyg. Assoc. J. 29:10-18.

Test Species/Strain/Number: 5 human subjects

Exposure Route/Concentrations/Durations: Inhalation: 10-100 ppm for various exposure durations.

Effects:

10 ppm for 15 min:	no eye, nose or respiratory irritation (basis for AEGL-1)
25 ppm for 5 min:	eye irritation
50 ppm for 3 min:	irritating to eyes, slightly irritating to nose
67 ppm for 1 min:	irritating to eyes and nose
100 ppm for 1 min:	very irritating to eyes and nose; subjects did not inhale

Endpoint/Concentration/Rationale: 10 ppm for 15 minutes resulted in no sensory irritation in healthy human subjects. Although this value is below the definition of an AEGL-1, it provides the longest exposure duration for which no irritation is reported. All studies indicated that fluorine is highly irritating and corrosive.

Uncertainty Factors/Rationale:

Total uncertainty factor: 3

Interspecies:	Not applicable, human subjects were tested
Intraspecies: 3-	The effect was a NOAEL for sensory irritation. Limited workplace monitoring data showed that workers exposed to fluorine at average yearly concentrations up to 1.2 ppm (range, 0.0-17 ppm) over a four-year period reported fewer incidences of respiratory complaints or diseases than a similar group of nonexposed workers (Lyon 1962). The workers are assumed to encompass a small range of sensitivity; the additional intraspecies uncertainty factor of 3 was considered sufficient to protect sensitive individuals.

Modifying Factor: 2 - to account for a limited data base.

Animal to Human Dosimetric Adjustment: Not applicable; human data used.

Time Scaling: Not applied; at mildly irritating concentrations, adaptation to sensory irritation occurs.

Data Adequacy: The key study was well conducted and documented; data in supporting studies were limited.

AEGL-2 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
20 ppm	**11 ppm**	**5.0 ppm**	**2.3 ppm**	**2.3 ppm**

Key Reference: Keplinger, M.L. and L.W. Suissa. 1968. Toxicity of fluorine short-term inhalation. Am. Ind. Hyg. Assoc. J. 29:10-18.

Test Species/Strain/Number: Swiss-Webster mice (sex not stated), 10/exposure group

Exposure Route/Concentrations/Durations:

Inhalation: 38, 79, 174, 300, 467, 600 ppm for 5 minutes
32, 65, 87, 188, 375 ppm for 15 minutes
16, 32, 67, 113, 225 ppm for 30 minutes
15, 30, 50, 75, 150 ppm for 1 hour

Effects (the 30-minute and 1-hour exposures were considered):

30-minute exposures:

16 ppm: no toxic signs, no gross lung pathology
32 ppm: no toxic signs, no gross lung pathology
67 ppm: no toxic signs, very mild diffuse lung congestion (basis for AEGL-2)
13 ppm: irritation and labored breathing, mild diffuse lung congestion
225 ppm: LC_{50}

1-hour exposures:

15 ppm: no toxic signs, no gross lung pathology
30 ppm: no toxic signs, very mild diffuse lung congestion (basis for AEGL-2)
50 ppm: labored breathing, mild diffuse lung congestion
75 ppm: irritation and labored breathing, severe diffuse lung congestion
150 ppm: LC_{50}

Endpoint/Concentration/Rationale: 67 ppm for 30 minutes and 30 ppm for 1 hour resulted in very mild diffuse lung congestion. Very mild lung congestion was considered the threshold for serious long-lasting effects such as severe lung congestion, seen at the next highest level tested.

Uncertainty Factors/Rationale:

Total uncertainty factor: 3

Interspecies: 1 - The effect (lung congestion) as well as LC_{50} values reported in the study were very similar for the rat, rabbit, and guinea pig (indicating similar species sensitivity). With the exception of the 5-minute LC_{50} value for the rabbit, the LC_{50} values for all four species at 15, 30, and 60 minutes were very similar.

Intraspecies: 3 - At the AEGL-2 concentrations, the effect of irritant gases is expected to be directly damaging to the tissues. The corrosive effect is not expected to differ greatly among individuals.

Modifying Factor: 2 - to account for a limited data base.

Animal to Human Dosimetric Adjustment: Not applied.

Time Scaling: $C^n \times t = k$ where $n = 1.77$; based on regression analysis of the mouse (the most sensitive species) LC_{50} data from the study conducted at 5, 15, 30, and 60 minutes (Keplinger and Suissa 1968). The 10-minute value was time scaled from the 30-minute value and the 4-hour value was time scaled from the 1-hour value. The 8-hour value was set equal to the 4-hour value because at low concentrations the hygroscopic fluorine would react with or be scrubbed by the nasal passages.

Data Adequacy: The key study was well conducted and documented; there were limited confirming data from other laboratories.

AEGL-3 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
36 ppm	**19 ppm**	**13 ppm**	**5.7 ppm**	**5.7 ppm**

Key Reference: Keplinger, M.L. and L.W. Suissa. 1968. Toxicity of fluorine short-term inhalation. Am. Ind. Hyg. Assoc. J. 29:10-18

Test Species/Strain/Number: Swiss-Webster mice (sex not stated), 10/exposure group

Exposure Route/Concentrations/Durations:

Inhalation: 38, 79, 174, 300, 467, 600 ppm for 5 minutes
32, 65, 87, 188, 375 ppm for 15 minutes
16, 32, 67, 113, 225 ppm for 30 minutes
5, 30, 50, 75, 150 ppm for 1 hour

Effects: The 1-hour substudy using the mouse was considered

15 ppm: no toxic signs, no gross lung pathology
30 ppm: no toxic signs, very mild diffuse lung congestion (basis for AEGL-2)
50 ppm: labored breathing, mild diffuse lung congestion
75 ppm: irritation and labored breathing, severe diffuse lung congestion
150 ppm: LC_{50}

Endpoint/Concentration/Rationale: 75 ppm for 1 hour resulted in irritation and labored breathing and severe diffuse lung congestion in the mouse. No deaths occurred. Severe diffuse lung congestion was considered the threshold for lethality.

Uncertainty Factors/Rationale:

Total uncertainty factor: 3

Interspecies: 1 - The effects (lung congestion) as well as LC_{50} values reported in the study were very similar for the rat, rabbit, and guinea pig (indicating similar species sensitivity). With the exception of the 5-minute LC_{50} for the rabbit, the LC_{50} values for all four species a t 15, 30, and 60 minutes were very similar. Thus, the concentration:endpoint did not differ greatly among species.

Intraspecies: 3 - Lung congestion at a specific concentration is not expected to differ greatly among individuals.

Modifying Factor: 2 - to account for a limited data base

Animal to Human Dosimetric Adjustment: Not applied.

Time Scaling: $C^n \times t = k$ where n = 1.77; based on regression analysis of the mouse (the most sensitive species) LC_{50} data from the study conducted at 5, 15, 30, and 60 minutes (Keplinger and Suissa 1968). The values were time scaled from the 1-hour data. The 8-hour value was set equal to the 4-hour value as was done for the AEGL-2. The safety of setting the 8-hour value equal to the 4-hour value is supported by another study in which a 7-hour exposure to 100 ppm resulted in an overall 60% mortality in four species (Eriksen 1945; Stockinger 1949). The time-scaled 7-hour LC_{50} values from the key study for the mouse (50 ppm) and rat (65 ppm) are lower.

Data Adequacy: The key study was well conducted and documented, but there were limited confirming data from other laboratories.